IMPROVED SOLID PHARMACEUTICAL DOSAGE FORMULATION OF HYDROPHOBIC DRUGS

Background of the Invention

The present invention relates to improved solid pharmaceutical dosage forms. In particular, the present invention is concerned with enhancing the dissolution of hydrophobic drugs.

Hydrophobic Drugs

As is well known, many pharmaceutically active compounds intended for oral administration are poorly soluble in water. Hydrophobic drugs do not generally dissolve easily and rapidly in the gastro-intestinal tract. This hydrophobic property often makes it difficult to formulate a drug so that it exhibits a satisfactory bioavailability profile in vivo. Poor bioavailability may lead to ineffective therapy, the need for higher dosing and/or undesirable side effects.

It has been recognized that the addition of a surfactant during the processing of a hydrophobic drug may improve the dissolution of the dosage units within the gastro-intestinal tract. Furthermore, for some hydrophobic drugs, the addition of a surfactant during processing may improve the bioavailability of the product due to improved wetting of the hydrophobic active ingredient, leading to faster dissolution and absorption.

Therefore, in order to compensate for the poor solubility of certain hydrophobic drugs, various carrier systems have been suggested wherein such drugs are co-formulated in intimate admixture with certain surfactants and other ingredients.

For example, U.S. Patent No. 4,344,934 discloses a mixture or solution of a poorly water-soluble drug with a pharmaceutically acceptable water-soluble polymer, wherein said mixture or solution has been treated with a minor amount of a wetting agent selected from anionic and cationic surfactants. Such compositions are formed as follows: First, a mixture or solution of the drug with the water-soluble polymer is formed. The mixture can be formed in a solvent or solvent mixture which is a mutual solvent for both the drug and the polymer. After the drug-polymer mixture or solution has been formed in a solvent, it is dried by spray-drying, flash evaporation or air drying. The powdered drug-polymer mixture is then treated with an amount of a primarily aqueous wetting solution containing a wetting agent selected from anionic and cationic surfactants. The treated mixture is then again dried and, if necessary, it is milled, screened or ground prior to formulating into suitable dosage forms with pharmaceutically acceptable excipients.

U.S. Patent No. 5,827,541 discloses a process for the preparation of an oral, rapidly disintegrating dosage form of a hydrophobic drug. The process comprises forming a suspension of the hydrophobic drug in a solvent containing a pharmaceutically acceptable surfactant together with a water-soluble or water-dispersible carrier material; forming discrete units of the suspension; and removing solvent from the discrete units under conditions whereby a network of the carrier material carrying a dosage of the hydrophobic drug is formed.

Thus, the common approach known in the art tends to focus on the development of carrier systems wherein the hydrophobic drug must be intimately admixed with the surfactant and other components. A serious disadvantage of this approach is that it has required the development, more or less empirically, of a separate carrier system for each hydrophobic drug. Also, admixing of wetting/solubilizing agents with the active ingredient can lead to product instability due to interaction between the drug and the wetting/solubilizing agent. The necessity to devise a separate carrier system for each drug is, of course, time-consuming and expensive. There continues to be a need for a single drug carrier system which is suitable for a wide range of different hydrophobic drugs.

Deposition of Drugs

A unique type of solid dosage form may be obtained by deposition of an active pharmaceutical ingredient on a pharmaceutically acceptable substrate. Various means for depositing pure active ingredients, such as weighing, spraying or spreading, can be used to generate the dosage form as taught, for example, in the following patents and patent publications, the disclosures of which are incorporated by reference herein in their entireties: U.S. Patent Nos. 5,845,463, 5,240,049, 5,018,335 and 4,640,322, as well as WO 00/09249, SU 1803328 and GB 2238768.

In a preferred embodiment, electrostatic deposition methodologies can be used. In the electrostatic deposition process, a cloud or stream of charged particles of the active ingredient is exposed to, or directed towards, a substrate, at the surface of which substrate a pattern of opposite charges has been established. In this fashion, a measured

dosage of the active ingredient can be adhered to the substrate. Preferred electrostatically deposited dosage forms are disclosed in published international patent application number WO 99/63972, assigned to the assignee of the present invention, the disclosure of which is incorporated by reference herein in its entirety.

Although electrostatic drug deposition generally has certain benefits, including improved dose uniformity, certain problems still arise when the drug to be electrostatically deposited is hydrophobic. Specifically, the final dosage form may suffer from the same problems of poor dissolution and poor bioavailability that were discussed above with respect to conventional solid dosage forms of hydrophobic drugs. Moreover, the prior art approach, involving the intimate admixture of the hydrophobic drug and a surfactant, would be difficult or impossible to implement in the context of electrostatic deposition.

For example, if the drug and surfactant powders are to be blended prior to electrostatic deposition on the substrate, it may be difficult to obtain a suitably homogenous blend, or to maintain such homogeneity during the charging and delivery to the substrate. Moreover, co-deposition of two different powders would require that both powders behave similarly during the deposition, but this is difficult to achieve since different powders often have different optimum deposition parameters. In an extreme case, the surfactant may deposit only under a charge opposite that utilized for the active ingredient.

One possible solution would be to deposit the active ingredient and the surfactant sequentially. However, there may be difficulty in forming depositions on top of pre-existing depositions, due to charge dissipation.

Therefore, it would be desirable to provide a dosage form of a hydrophobic drug, wherein the problems of poor solubility and poor bioavailability, as well as the technical problems identified in the preceding paragraphs, are overcome.

Summary of the Invention

In accordance with the teachings of the present invention, improved solid pharmaceutical dosage formulations are provided, characterized by the enhanced dissolution of hydrophobic drugs. The formulations comprise:

a base substrate comprising a first polymer;

a deposit, comprising a therapeutic amount of a hydrophobic drug, deposited on the base substrate;

a cover substrate comprising a second polymer, the cover substrate covering the deposit and joined to the base substrate by a bond that surrounds the deposit; and

a dissolution-enhancing amount of a surfactant, disposed within a carrier that is segregated from, but in contact with, the deposit.

It is accordingly an object of the present invention to provide solid pharmaceutical dosage formulations of hydrophobic drugs having enhanced dissolution and improved bioavailability.

Brief Description of the Drawings

FIG. 1 depicts an isometric view of a product comprising a strip package containing a plurality of unit forms in accordance with the prior art.

FIG. 2 depicts a cover layer of a prior art strip package partially separated from a substrate.

FIG. 3 depicts a side view of an illustrative unit form in accordance with the prior art.

FIG. 4 depicts a top view of the illustrative unit form of FIG. 3.

FIG. 5 depicts components of various embodiments of unit forms of the present invention.

FIG. 6 is a graph of dissolution profiles for the drug CCN00401.

FIG. 7 is a graph of dissolution profiles for the drug hydrocortisone.

FIG. 8 is a graph of dissolution profiles for the drug glipizide.

Detailed Description of the Invention

FIGS. 1 through 4 depict the general structure of prior art dosage forms which are to be improved in accordance with the present invention. In FIG. 1, product **1** comprises a package **2** that is realized as a strip **4** having an array of unit dosage forms **6**. Strip **4** comprises a substrate **8** and a cover layer **9**.

Substrate **8** and cover layer **9** each comprise a substantially planar, flexible film or sheet. In some embodiments, one of either substrate **8** or cover layer **9** includes an array of semi-spherical bubbles, concavities, blisters or depressions (hereinafter "bubbles") **12** that are advantageously arranged in columns and rows. In the illustrative package depicted in FIG. 1, cover layer **9** comprises a three-by-five array of such bubbles **12**, although more or fewer bubbles may suitably be provided. Substrate **8** and cover layer **9** are advantageously formed to have a thickness of about 0.001 inches (0.0254 mm) and typically comprise a thermoplastic material. Materials suitable for use as substrate **8** and/or cover layer **9** include, without limitation, polymers and copolymers of polyvinyl alcohol, polyvinyl pyrrolidinone, polysaccharide polymers, acrylate polymers, methacrylate polymers, phthalate polymers, polyvinyl acetate, methyl cellulose, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose,

hydroxypropylmethylcellulose, ethyl cellulose, polyethylene oxide, polypropylene, polyester and polyamide films, Eudragits (that is, polymers and copolymers containing methacrylic acid), starch-based polymers, gelatin and the like. Polyvinyl alcohol films suitable for use as the substrate and/or cover layer are commercially available from Polymer Films, Inc. of West Haven, CT; Chris Craft of Gary, IN; Aquafilm of Winston-Salem, NC; Idroplast S.p.A. of Montecatini Terme (PT), Italy; Aicello Chemical Co., Ltd. of Toyohashi; Japan; and Soltec of Paris, France.

As depicted in FIG. 2 (showing cover layer 9 partially "peeled" back from substrate **8**) and FIG. 3, a deposit of a dry active ingredient **14**, in the form of powder(s)/grains (hereinafter, "powder") is disposed between substrate **8** and cover layer **9** within a bubble **12**. Active ingredient **14** is deposited on substrate **8**. As depicted via a cross-sectional view in FIG. 3 and plan view in FIG. 4 (each showing only a single bubble **12**), substrate **8** and cover layer **9** are attached to one another via bonds or welds **7** that are near to and encircle bubble **12**. Bonding can be effected, for example, via heat or ultrasonic welding or via suitable adhesives. Unit form **6** comprises a deposit of active ingredient **14**, bubble **12**, and a region of substrate **8** within bonds **7**. Unit form **6** is a stable "core" (hereinafter, an "Accudep™ Core"), which may be further processed into a dosage form resembling a conventional tablet, capsule, caplet and the like or processed into a non-conventional wafer or stamp-like presentation. The preferred dosage forms may be suitable for oral, transdermal or buccal dosing of appropriate drugs.

Suitable means of electrostatic deposition of active ingredient **14** are described in, for example, U.S. Patent Nos. 5,714,007, 5,846,595 and 6,074,688, the disclosures of which are incorporated by reference herein in their entireties. In addition

to the electrostatic powder cloud deposition method, active ingredient may be coated onto the substrate in the form of a solution or a suspension of finely divided medicament; e.g., a collodial suspension. The liquid utilized for these operations can be water, an organic solvent, e.g., ethanol, or a hydroalcoholic solvent. One method of loading active ingredient in a liquid form onto a substrate is by electrostatic jet spray deposition. In this method, the active ingredient containing solution or suspension is metered into an apparatus which projects a spray of microdroplets which are concentrated on a particular area of the substrate through the use of a defined area electrostatic field.

In addition to electrostatic jet spray deposition, certain other coating techniques recognized in other arts as being amenable to the coating of a substrate with a liquid may be utilized in loading a pharmaceutically acceptable substrate with active ingredient. For example, the substrate may be passed under a roll which is immersed in a bath of saturating fluid. As the substrate passes the roller, the excess fluid is "wiped" from the substrate by another roller, a jet of air, a rubber wiping bar, a wire-wound rod, e.g., a Meier rod, or the like.

The present invention improves upon the prior art dosage forms depicted in FIGS. 1 through 4 by providing a dissolution-enhancing amount of a surfactant, disposed within a carrier that is segregated from, but in contact with, the active ingredient. The invention is based on the surprising finding that, contrary to the teachings in the prior art, a surfactant can improve the dissolution (and, consequently, the bioavailability) of a hydrophobic drug even though the drug and the surfactant are not co-formulated in intimate admixture with one another.

Certain embodiments of the present invention are depicted in FIG. 5. In the drawing with the legend "Deposition," active ingredient ("drug") **14** is shown after being deposited on substrate **8**, prior to sealing with cover layer **9**. In the first drawing with the legend "Cover Film" ("Surfactant in Pouch"), the surfactant is incorporated on the cover layer ("cover film") **9** in a pouch **16**, and cover layer **9** is aligned to place the pouch **16** in contact with active ingredient **14**. The pouch material may be any polymer, and preferably the same material as substrate **8** or cover layer **9**. Upon administration of the dosage form, during dissolution of cover layer **9** and/or substrate **8**, pouch **16** similarly dissolves and releases the surfactant in the immediate vicinity of the drug, thereby improving drug dissolution.

An alternative embodiment of the present invention is depicted in the second drawing in FIG. 5 with the legend "Cover Film" ("Surfactant in Adhesive"). In this embodiment, the surfactant is incorporated in an ingestible adhesive **10** that is applied to cover layer **9**. After sealing cover layer **9** to substrate **8**, the surfactant is in contact with, but segregated from, active ingredient **14**. Upon administration of the dosage form and dissolution of cover layer **9** and/or substrate **8**, the adhesive dissolves and releases the surfactant in the immediate vicinity of the drug, again improving drug dissolution.

In a preferred embodiment (not specifically shown in FIG. 5), neither a pouch **16** nor a special adhesive **10** is required. Rather, the surfactant is incorporated directly in cover layer **9**, so that the dissolving cover layer **9** releases the surfactant in the immediate vicinity of the encapsulated hydrophobic drug, allowing the surfactant to interact with the drug to help with dissolution.

In the context of the present invention, "hydrophobic drug" means a drug that ranges from "sparingly soluble" to "practically insoluble or insoluble," as shown in the following table:

Descriptive Term	Parts of Solvent Required For 1 Part of Solute
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

The hydrophobic drugs, and their pharmaceutically acceptable salts, which may be formulated in accordance with the present invention include, without limitation, the following:

Analgesics and anti-inflammatory agents: acetaminophen, aloxiprin, auranofin, azapropazone, benorylate, celecoxib, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, rofecoxib, salicylamide, salicylic acid, sulindac.

Anthelmintics: albendazole, bephenium hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxantel embonate, oxfendazole, praziquantel, pyrantel embonate, thiabendazole.

Anti-arrhythmic agents: amiodarone, disopyramide, flecainide, quinidine.

Anti-bacterial agents: benethamine, cefaclor, cinoxacin, ciprofloxacin, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin, penicillin, rifampicin, spiramycin,

sulphabenzamide, sulphacetamide, sulphadiazine, sulphadoxine, sulphafurazole, sulphamerazine, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim.

Anti-coagulants: dicoumarol, dipyridamole, nicoumalone, phenindione.

Anti-depressants: amoxapine, maprotiline, mianserin, nortriptyline, oxypertine, trazodone, trimipramine.

Anti-diabetics: acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, tolbutamide.

Anti-epileptics: beclamide, carbamazepine, clonazepam, ethotoin, metharbital, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phensuximide, phenytoin, primidone, sulthiame, valproic acid.

Anti-fungal agents: amphotericin, butoconazole, clotrimazole, econazole, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole, terbinafine, terconazole, tioconazole, undecenoic acid.

Anti-gout agents: allopurinol, probenecid, sulphinpyrazone.

Anti-hypertensive agents: amlodipine, benidipine, darodipine, diazoxide, dilitazem, felodipine, guanabenz, isradipine, methyldopa, minoxidil, nicardipine, nifedipine, nimodipine, phenoxybenzamine, prazosin, reserpine, terazosin.

Anti-malarials: amodiaquine, chloroquine, chlorproguanil, halofantrine, mefloquine, proguanil, pyrimethamine, quinine.

Anti-migraine agents: dihydroergotamine, ergotamine, methysergide, pizotifen, sumatriptan.

Anti-muscarinic agents: atropine, benzhexol, biperiden, ethopropazine, hyoscyamine, mepenzolate, oxyphencylcimine, tropicamide.

Anti-neoplastic agents and immunosuppressants: aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, finasteride, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazine, raloxifene, tamoxifen, testolactone.

Anti-Parkinsonian agents: bromocriptine, lysuride.

Anti-protazoal agents: benznidazole, clioquinol, decoquinate, diiodohydroxyquinoline, diloxanide, dinitolmide, furzolidone, metronidazole, nimorazole, nitrofurazone, ornidazole, tinidazole.

Anti-thyroid agents: carbimazole, propylthiouracil.

Anxiolytics, sedatives, hypnotics and neuroleptics: allobarbitone, allylbarbituric acid, alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, carphenazine, chlordiazepoxide, chlormethiazole, chlorpromazine, clobazam, clotiazepam, clozapine, cyclobarbitone, diazepam, droperidol, ethinamate, flunanisone, flunitrazepam, fluopromazine, flupenthixol, fluphenazine, flurazepam, haloperidol, lorazepam, lormetazepam, medazepam, meprobamate, methaqualone, midazolam, nitrazepam, oxazepam, pentobarbitone, perphenazine, pimozide, prochlorperazine, sulpiride, temazepam, thioridazine, triazolam, zopiclone.

β-Blockers: acebutolol, alprenolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol.

Cardiac Inotropic agents: amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin.

Corticosteroids: beclomethasone, betamethasone, budesonide, cortisone, desoxymethasone, dexamethasone, flucortolone, fludrocortisone, flunisolide, fluticasone,

hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.

Diuretics: acetazolamide, amiloride, amisometradine, bendroflumethiazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, metolazone, spironolactone, triamterene.

Gastro-intestinal agents: aminosalicylic acid, bisacodyl, cimetidine, cisapride, diphenoxylate, domperidone, famotidine, loperamide, mesalazine, nizatidine, omeprazole, ondansetron, ranitidine, sulphasalazine.

Histamine H_1-Receptor Antagonists: acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadine, dimenhydrinate, fexofenadine, flunarizine, loratadine, meclozine, oxatomide.

Lipid-regulating agents: atorvastatin, bezafibrate, clofibrate, dextrothyroxine, fenofibrate, gemfibrozil, lovastatin, probucol, simvastatin.

Nitrates and other anti-anginal agents: amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate.

Nutritional agents: betacarotene, vitamin A, vitamin B, vitamin D, vitamin E, vitamin K.

Opioid analgesics: codeine, dextropropyoxyphene, diamorphine, dihydrocodeine, meptazinol, methadone, morphine, nalbuphine, pentazocine.

Respiratory agents: montelukast, pranlukast (CCN00401), zafirlukast, zileuton.

Sex hormones: clomiphene, conjugated estrogens, danazol, estradiol, ethinyloestradiol, medrogestone, medroxyprogesterone acetate, mestranol, methyltestosterone, norethisterone, norgestimate, norgestrel, progesterone, stanozolol, stiboestrol, testosterone, tibolone.

Stimulants: amphetamine, cocaine, dexamphetamine, dexfenfluramine, fenfluramine, mazindol.

Thyroid agents: levothyroxine.

By "surfactant" is meant, for purposes of the present invention, that the material is a surface active agent which displays wetting, detergent or soap-like qualities as those agents are understood by those of ordinary skill in the art. Thus, the term "surfactant," as used herein, represents ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, such as ethoxylated castor oil, benzalkonium chloride, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium lauryl sulfate, magnesium lauryl sulfate, triethanolamine, cetrimide, sucrose laurate and other sucrose esters, glucose (dextrose) esters, simethicone, ocoxynol, dioctyl sodium sulfosuccinate, polyglycolyzed glycerides, sodium dodecylbenzene sulfonate, dialkyl sodium sulfosuccinate, fatty alcohols such as lauryl, cetyl, and steryl, glycerylesters, cholic acid or derivatives thereof, lecithins, and phospholipids.

The surfactants of the invention may be classified by an "HLB number." The HLB number provides a means for ranking surfactants based on the balance between the hydrophilic and lipophilic portions of the surfactant. That is, the higher the HLB number, the more hydrophilic the surfactant.

In a broader implementation of the present invention, many other types of pharmaceutical additives (instead of, or in addition to, the surfactant) may be included in the dosage form disposed within a carrier that is segregated from, but in contact with, the deposited active ingredient. Such pharmaceutically acceptable additives include, but are not limited to, antioxidants, antimicrobial agents, complexing agents, acidity boosting agents, alkalinity boosting agents, buffering agents, carrier molecules, chelating compounds, preservatives and the like. "Pharmaceutically acceptable" here means that the additive may be introduced safely into the human or animal body, for example, taken orally and digested. Examples of such additives include, but are not limited to, the following:

<u>Acidifying agents:</u> citric acid, maleic acid, lactic acid, malic acid, succinic acid, tartaric acid.

<u>Alkalinity buffering agents:</u> calcium carbonate, monoethanolamine, potassium citrate, sodium bicarbonate, sodium citrate, triethanolamine.

<u>Anti-microbial agents:</u> benzethonium chloride, benzoic acid, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, editic acid, ethylparaben, glycerol, imidurea, methylparaben, phenol, phenolic acid, phenoxyethanol, phenyl ethyl alcohol, phenylmercuric salts (acetate, borate and nitrate), potassium sorbate, propylene glycol, propylparaben, sodium benzoate, sodium propionate, sorbic acid, thimerosol.

<u>Anti-oxidants:</u> alpha tocopherol, ascorbic acid, ascorbic acid palmitate, butylated hydroxyanisole, fumaric acid, malic acid, propyl gallate, sodium ascorbate, sodium metabisulfate.

<u>Complexing agents</u>: EDTA, potassium citrate, sodium citrate.

EXAMPLES

The following materials were used in the Examples:

Hydroxypropylmethylcellulose E50 ("HPMC"), available from Dow Chemical Company, Midland, Michigan.

Hydroxypropylcellulose JFP ("HPC"), available from Hercules Inc., Wilmington, Delaware.

Polyethylene Glycol 400 ("PEG"), available from Union Carbide Corporation, Danbury, Connecticut

Sodium lauryl sulfate ("SLS"), HLB = 40, available from Spectrum Quality Products, New Brunswick, New Jersey

Polysorbate 80 (Tween 80), HLB = 15, available from Uniqema, a division of ICI, Wilmington, Delaware

Polysorbate 20 (Tween 20), HLB= 16.7, available from Uniqema

Hydrocortisone, available from Spectrum Quality Products

Glipizide, available from Fine Chemicals Corporation, Capetown, South Africa.

Example 1

A model compound, CCN00401, was used to test the effect sodium lauryl sulfate (SLS) has on dissolution of an Accudep™ Core. Several types of Accudep™ Cores were made as follows:

Control Accudep™ Core: Sealed a 1 mg deposition of CCN00401 between two polymer sheets with the following composition: 45% HPMC, 45% HPC, 10% PEG.

SLS incorporated in film Accudep™ Core: Sealed a 1 mg deposition of CCN00401 between two polymer sheets with the following composition: 33.75% HPMC, 33.75% HPC, 7.5% PEG, 25% SLS (equivalent of about 1.2 mg SLS incorporated in each Accudep™ Core).

SLS mixed directly with CCN00401 Accudep™ Core: Sealed mixture of 2 mg of CCN00401/SLS mixture (50/50) between two polymer sheets with the following composition: 45% HPMC, 45% HPC, 10% PEG.

Dissolution profiles for the Accudep™ Cores listed above were generated under the following conditions: 50 rpm, paddles, pH 8.0 TRIS buffer. In addition, a set of Control Accudep™ Cores were tested in dissolution media that also contained Polysorbate 20.

Fig. 6 shows the average dissolution profiles for all the CCN00401 dissolution runs (n=3). As seen in Fig. 6, the addition of SLS in the polymer film or mixed directly with the drug led to significantly faster dissolution at 15 minutes (even faster than the case where Polysorbate 20 is present in the media). At 30 minutes all

experimental sets had average dissolution in the mid-to-high 90% range except for the case with no surfactant in Accudep™ Core or dissolution media.

Example 2

Hydrocortisone, CCN90306A, was used to test the effect SLS and Polysorbate 80 have on dissolution of an Accudep™ Core. Accudep™ Cores were made as follows:

Control Accudep™ Core: Sealed a 1 mg deposition of CCN90306A between two polymer sheets with the following composition: 45% HPMC, 45% HPC, 10% PEG.

SLS incorporated in film Accudep™ Core: Sealed a 1 mg deposition of CCN90306A between two polymer sheets with the following composition: 36% HPMC, 36% HPC, 8% PEG, 20% SLS (equivalent of about 5 mg SLS incorporated in each Accudep™ Core).

Polysorbate 80 incorporated in film Accudep™ Core: Sealed a 1 mg deposition of CCN90306A between two polymer sheets with the following composition: 36% HPMC, 36% HPC, 8% PEG, 20% Polysorbate 80 (equivalent of about 5 mg Polysorbate 80 incorporated in each Accudep™ Core).

Dissolution profiles for the Accudep™ Cores listed above were generated under the following conditions: 75 rpm, paddles, distilled water.

Fig. 7 shows the average dissolution profiles for all the CCN90306A dissolution runs (n=3). As seen in Fig. 7, the addition of SLS and Polysorbate in the polymer film led to faster dissolution at 20- and 30-minute sample points.

Example 3

Glipizide, CCN90906A, was used to test the effect SLS and Polysorbate 80 have on dissolution of an Accudep™ Core. Accudep™ Cores were made as follows:

SLS incorporated in film Accudep™ Core: Sealed a 1 mg deposition of CCN90906A between two polymer sheets with the following composition: 36% HPMC, 36% HPC, 8% PEG, 20% SLS (equivalent of about 5 mg SLS incorporated in each Accudep™ Core).

Polysorbate 80 incorporated in film Accudep™ Core: Sealed a 1 mg deposition of CCN90906A between two polymer sheets with the following composition: 36% HPMC, 36% HPC, 8% PEG, 20% Polysorbate 80 (equivalent of about 5 mg Polysorbate 80 incorporated in each Accudep™ Core).

Dissolution profiles for the Accudep™ Cores listed above were generated under the following conditions: 50 rpm, paddles, simulated intestinal fluid.

Fig. 8 shows the average dissolution profiles for all the CCN90906A dissolution runs (n=6). As seen in Fig. 8, the addition of SLS and Polysorbate in the polymer film led to faster dissolution, especially during the first 60 minutes.

Although the present invention has been described with particular reference to certain preferred embodiments thereof, variations and modifications of the present invention can be effected within the spirit and scope of the following claims.